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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,717	07/14/2006	Dan Gazit	30695	6234

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
10/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,717	GAZIT ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/18/2007,7/11/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87,90,92,94,95,97,99-102,104,112,113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87,90,92,94,95,97,99-102,104,112,113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/29/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group II (Claims 87, 88, 90, 92, 94, 95, 97, 99-102 and SEQ ID NO: 3 and 11) in the reply filed on 7/17/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

In view of the cancellation of non-elected subject matter, no claims are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/18/07.

Information Disclosure Statement

The examiner has considered the international search report.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 87, 90, 92, 94, 97, 99-102, 104 and 112-113 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The GenBank Accession number NM_145331, SEQ ID NO: 11 in claims 87, 90, 94, 95, and 97 and claims dependent therefrom does not comply with the written description requirement because citing the accession number is improper incorporation of reference of essential subject matter into the claims. The accession number is considered essential matter required for one skilled in the art to practice the claimed method. See Zenon Environmental, Inc. v. United States Filter Corp United States Court of Appeals for the Federal Circuit, Case No. 06-1266, 11/17/2007. Also see MPEP 608.01(p) states:

> A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. In re Glass, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention.
>
> Specific operative embodiments or examples of the invention must be set forth.

Written Description rejection:

Claims 87, 92, 94, 95, 99-102, and 104 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention set forth in claims 87 and 94 and claims dependent therefrom is drawn to a method of modulating an activity of a SMAD protein in a cell comprising contacting the cell with a genus of agents capable of diminishing an expression and/or activity of TAK! as set forth in SEQ ID NO: 11 in the cell. The instant claims are broadly drawn to a genus of agents capable of diminishing an expression and/or activity of TAK1 and read on a method of increasing or decreasing an activity of a SMAD protein using of agents. The claims are not limited to any SMAD protein or any SMAD protein from any particular cell, reading on a large number of agents that diminishes an expression and/or activity of TAK1 from any source, that will function, as an agent to modulate an activity of a SMAD protein from any source.

The specification as filed does not provide an adequate written description of the vast genus of agents, that will function, commensurate with the breadth of what is claimed, as agent to modulate (reduce or induce, for example) the activity of a SMAD protein.

The specification as filed provides description or limiting definition of what is encompassed by an agent capable of diminishing or abrogating expression and/or

activity of TAK1. The specification provides description or limiting definition of what is encompassed by SMAD protein. The specification discloses minimal examples of methods of making siRNAs as claimed (pages 20-21). To date there are at least eight types of SMAD. Neither the specification nor the prior art sufficiently disclose agents that possesses the desired biological activity as recited in the claims. The specification only describes siRNA for human TAK1 that meets the functional limitations of the claimed invention. Thus, there a variation within the species embraced by the genus of nucleotide sequences and the skilled artisan would be required to further experiment to determine what agent meets the structural and functional limitations of the claim agents.

Therefore, in disclosing only broad and general guidance in regards to what is claimed, which is a method of using an agent that will function in a genus of cells, commensurate with the breadth of what is claimed, as to modulate (reduce or induce, for example) the expression of that selected target gene and only limited examples of the claimed agent, the specification does not provide a representative number of species of the method of using, as claimed, that would be sufficient to show possession of the vast genus claimed.

The specification does not provide the specific description that would be required to reasonably lead one of skill in the art to the instant invention or that would allow the skilled artisan to recognize that Applicant was in possession of the instant invention. The specification does not disclose how to make a representative number of species of the claimed genus with the desired biological function. See Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996). .

MPEP § 2163[R-2] I. states:

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., > Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003);< Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116.

The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc., 935 F.2d at 1563-64, 19 USPQ2d at 1117.

Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such

characteristics. > Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613.<

In the instant case, Applicant has not provided adequate written description of their invention because the specification does not convey, with reasonable clarity to those of skill in the art, as of the filing date sought, that applicant was in possession of the invention now claimed. Applicant has not shown how the invention was "ready for patenting" such as by the disclosure of a method as claimed, that made an genus of agents that diminish an expression and/or activity of TAK1, that will function, commensurate with the breadth of what is claimed, as to modulate (reduce or induce, for example) the activity of a SMAD protein, for example.

Claims 87, 90, 92, 94, 95, 97, 99-102, 104, and 112-113 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

With respect to method in claims 87 and claims dependent therefrom, the method reads on increasing or decreasing activity of a SMAD proteins in a cell comprising contacting the cell with an agent that diminishes or abrogates an expression and/or activity of TAK1 in the cell, thereby regulating the activity of the SMAD protein in the cell. However, in the view of the guidance in the specification, the only intended use for the method in claims 87 and claims dependent therefrom is the method set forth in claim 94 and claims dependent therefrom.

In addition, the claimed method reads on using a genus of cells, SMAD proteins and agents. In addition, the claimed method embraces decreasing or increasing a genus of activities of a SMAD protein. Thus, the claims are considered broad.

.At about the effective filing date of the present application (4/1/2003), virtually nothing was known on the use of ().

The applicants discuss TGF-beta kinase (TAK1) and SMAD proteins (pages 1-2). Applicants teach that, "the molecular events in TAK1 involved signaling cascades, in particularly early events in the cascade are as yet not well defined (page 1)." There are at least eight SMAD proteins. SMAD1, SMAD5, and SMAD8 proteins are activated by bone morphogenetic protein (BMP). SMAD2 and SMAD3 proteins activate TGF-beta and SMAD 6 and 7 proteins inhibit intracellular signaling by R-SMAD/SMAD4. In view of the intended use of the claimed invention, it is not apparent how several of the SMAD proteins could be used in the method since they are not involved in BMP-mediated SMAD activity resulting in osteogenesis and/or bone repair.

Apart from the exemplification showing that in mouse embryonic mesenchymal C3H10T1/2 stem cells gave rise to efficient osteogenic differentiation *in vitro*, the instant specification fails to provide sufficient guidance for a skilled artisan on how to use any transfected cell types for repairing or for forming bone in a subject in need thereof. It is not clear whether diminishing or abrogating an expression and/or activity of TAK1 could exert the same effects (e.g., proliferation and osteogenic differentiation) on cell types other than mesenchymal stem cells as those obtained for mouse embryonic mesenchymal stem cells to yield the desired therapeutic effects. It should be noted that TAK1 and SMAD seem to be involved in different pathways and do not interact with one another in cells (Sano et al. (The Journal of Biological Chemistry 274:8949-8957, 1999) and Shim et al. (Genes and Development 19: 2668-2681, 2005)). At the effective filing date of the present application, there was still a need to understand how TAK1 exert different effects as well as to identify their target genes. Since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the present application to do so.

The physiological art is recognized as unpredictable (MPEP 2164.03). Given the state of the prior art as already discussed above, coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the method and composition as claimed.

Furthermore, with respect to the method claims the instant specification fails to provide sufficient guidance for a skilled artisan on how to repair or forming a bone in a

subject in need by administering the engineered cell or targeting cells at any site in the subject. There is no evidence of record indicating that any genetically modified cell of the presently claimed invention is capable of targeting to any site in need of repairing or forming a bone in a subject. Once again, since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the instant specification to do so. With the lack of sufficient guidance provided by this disclosure, it would have required undue experimentation for a skilled artisan to make and use the method as broadly claimed.

Apart from the exemplification showing that only control embryonic mouse mesenchymal C3H10T1/2-BMP2 and TAK1dn stem cells were ALP-positive (osteoblast-like) *in vitro*, indicating that activated endogenous TAK1 negatively impacts osteogenic differentiation, the instant specification fails to provide any other examples showing that diminishing or abrogating an expression and/or activity of TAK1 is effective in inducing osteogenic differentiation in mesenchymal stem cells *in vivo*. Nor does the instant disclosure provide any other examples showing that TAK1dn over-expressing C3H10T1/2BMP2 cells is also effective in inducing osteogenic differentiation in any other cell types in either *in vitro* or *in vivo* to yield the therapeutic effects contemplated by Applicants.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the relevant art on cells genetically modified to diminish or abrogate an expression and/or activity of TAK1 to repair or forming a bone in a subject in need, and the breadth of the claims, it would

have required undue experimentation for one skilled in the art to **make and use** the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 87, 90, 92, 94, 95, 97, 99-102, 104, and 112-113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "TAK1 (GenBank Accession number: NM_145331, SEQ ID NO: 11)" in claims 87, 90, 92, 94, 95, 97, 99-102, 104, and 112-113 is a relative term, which renders the claims indefinite. The term " TAK1 (GenBank Accession number: NM_145331, SEQ ID NO: 11)" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of the term are undefined because it is not apparent if the term in parenthesis is an example of the nucleic acid molecule or is the nucleic acid molecule. Suggest amending the phrase to recite "TAK1 as set forth in SEQ ID NO: 11."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 87 embraces a method of regulating the activity of a SMAD protein in a genus of cells comprising contacting a cell with an agent that diminishes expression and/or activity of TAK1 as set forth in SEQ ID NO: 11 in the cell, thereby regulating the activity of the SMAD protein in the cell. The method reads on using any agent that indirectly or directly regulates the activity of a SMAD protein and that indirectly or directly inhibits expression and/or activity of TAK1.

Claims 87 and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bartelmez et al. (US 6,841,542) taken with (Sugita et al., WO 99/40202, of record) in further view of Sano et al. (The Journal of Biological Chemistry 274:8949-8957, 1999). Bartelmez teaches using an antisense oligomer to inhibit type I and type II TGF-beta in cells (columns 9-11). However, Bartelmez does not specifically teach the cells comprising SEQ ID NO: 11.

However, at the time the invention was made, Sugita teaches a nucleic acid sequence encoding TAK-1, wherein the sequence comprises SEQ ID NO: 11 is located in cells (pages 39-43). Since the protein is found in human cells, it would have been obvious to one of ordinary skill in the art that human cells comprise a nucleotide sequence comprising SEQ ID NO: 11.

In addition, at the time the invention was made, Sano teaches that type I and type II TGF-beta is upstream of pathways containing TAK1 and SMAD proteins (page 8955, Figure 8). Thus, one of ordinary skill in the art would reasonably expect that by inhibiting either TGF-beta type I or II would result in modulating an activity of a SMAD protein and expression and/or activity of TAK-1 in a cell.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of taken with Sugita in further view of Sano, namely to inhibit an activity of a SMAP protein and expression and/or activity of TAK1 as set forth in SEQ ID NO: 11 in a cell. One of ordinary skill in the art would have been motivated to combine the teaching to regulate the differentiation of stem cells in vitro. "The combination of familiar elements according to known methods

is likely to be obvious when it does no more than yield predictable results." See ***KSR v. Teleflex***, 550 U.S. ___, 127 S. Ct. 1727 (2007).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 6:30 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, SPE – Art Unit 1635, can be reached at (571) 272-0763.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Brian Whiteman/
Primary Examiner, Art Unit 1635